II. REMARKS

Formal Matters

Claims 1, 2, 7-10, and 24-27 are pending after entry of the amendments set forth herein.

Claims 1, 2, 7-10, and 24-27 were examined and were rejected. Claims 3-6 and 11-23 were withdrawn from consideration.

Claims 1, 25, and 27 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. The amendment to claim 25 is editorial in nature; accordingly, no new matter is added by the amendment to claims 25. Support for the amendments to claims 1 and 27 is found in the claims as originally filed, and throughout the specification, in particular at the following locations: claim 1: page 7, lines 16-21; and page 8, lines 15-24; and claim 27: page 12, lines 3-11. Accordingly, no new matter is added by these amendments.

Claims 3-6 and 11-24 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Claim objections

Claim 25 was objected to for reciting "monoacylglycerol transferase activity."

Claim 25 is amended to recite "monoacylglycerol acyltransferase activity," thereby adequately addressing this objection.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1, 2, 7-10, and 24-27 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

The final Office Action stated that the specification does not reasonably provide enablement for any polynucleotide which encodes a polypeptide that exhibits diacylglyceraol acyltransferase activity

wherein said polynucleotide "has a mere 90% identity to SEQ ID NO:3." Final Office Action, page 3. Applicants respectfully traverse the rejection.

Comments regarding the instant specification

The instant specification provides nucleotide sequences of several polynucleotides that comprise nucleotide sequences encoding polypeptides that exhibit monoacylglycerol acyltransferase activity, diacylglycerol acyltransferase activity, or both monoacylglycerol acyltransferase and diacylglycerol acyltransferase activity. The specification provides SEQ ID NOs:01, 03, 05, 07, 09, 11, 13, and 15, which comprise nucleotide sequences encoding polypeptides having amino acid sequences as set forth in SEQ ID NOs:02, 04, 06, 08, 10, 12, 14, and 16, respectively. Specification, page 8, lines 15-24; and page 12, lines 3-21. Thus, the instant specification provides at least **eight** different polynucleotides that comprise nucleotide sequences encoding a polypeptide that exhibits monoacylglycerol and/or diacylglycerol acyltransferase activity.

The instant specification provides descriptions of how to determine whether a given polypeptide exhibits monoacylglycerol and/or diacylglycerol acyltransferase activity. For example, the specification describes an assay which includes the polypeptide, an acyl donor, and an acyl acceptor. Specification, page 24, lines 11-23. Whether a polypeptide exhibits monoacylglycerol acyltransferase (MGAT) activity is determined using a monoacylglycerol as the acyl acceptor; likewise, whether a polypeptide exhibits diacylglycerol acyltransferase (DGAT) activity is determined using a diacylglycerol as the acyl acceptor. Specification, page 24, lines 11-23.

The Examples section provides working examples of how to determine whether a given polypeptide exhibits monoacylglycerol and/or diacylglycerol acyltransferase activity. For example, mouse DGAT2α (SEQ ID NO:4) was produced in insect cells, and tested for DGAT activity. Specification, page 43, line 22 to page 44, line 16.

Additional working examples of measuring DGAT and MGAT activity are provided in Example 5. Specification, page 46, line 11 to page 47, line 10. For example, the enzymatic activity of MGAT polypeptides (e.g., SEQ ID NOs:06) were assayed. Example 5.

Comments regarding the "Wands" factors

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled

with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

As discussed above, the instant specification teaches a) the nucleotide sequences of several polynucleotides comprising nucleotide sequences encoding polypeptides that exhibit monoacylglycerol acyltransferase activity, diacylglycerol acyltransferase activity, or both monoacylglycerol acyltransferase and diacylglycerol acyltransferase activity; b) detailed assays for how to determine whether a given polypeptide exhibits monoacylglycerol and/or diacylglycerol acyltransferase activity; c) working examples of polypeptides, encoded by subject polynucleotides, that exhibit monoacylglycerol and/or diacylglycerol acyltransferase activity.

Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

(a) the quantity of experimentation necessary:

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of

[1] *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

[2] *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

[3] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

[4] *In re Wands* 8 USPQ 2d at 1404

guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.[5]

The claimed compositions recite polynucleotides comprising nucleotide sequences that encode polypeptides that exhibit monoacylglycerol and/or diacylglycerol acyltransferase activity. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which sequences retain the ability to encode polypeptides that exhibit monoacylglycerol and/or diacylglycerol acyltransferase activity. The sequence of polypeptides retaining biological activity is determined through routine experimentation, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants of the polypeptide made by routine recombinant DNA techniques. Since these experiments are routine in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay on polypeptide variants to determine the active variants, no undue experimentation is necessary.

(b) the amount of direction or guidance presented

As discussed in detail above, the instant specification teaches a) the nucleotide sequences of several polynucleotides comprising nucleotide sequences encoding polypeptides that exhibit monoacylglycerol acyltransferase activity, diacylglycerol acyltransferase activity, or both monoacylglycerol acyltransferase and diacylglycerol acyltransferase activity; b) detailed assays for how to determine whether a given polypeptide exhibits monoacylglycerol and/or diacylglycerol acyltransferase activity; c) working examples of polypeptides, encoded by subject polynucleotides, that exhibit monoacylglycerol and/or diacylglycerol acyltransferase activity.

[5] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

(c) the presence or absence of working examples:

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7]

Nevertheless, as discussed above, the instant specification provides working examples of measuring monoacylglycerol acyltransferase activity and diacylglycerol acyltransferase activity. The Examples section provides working examples of how to determine whether a given polypeptide exhibits monoacylglycerol and/or diacylglycerol acyltransferase activity. For example, mouse DGAT2α (SEQ ID NO:4) was produced in insect cells, and tested for DGAT activity. Specification, page 43, line 22 to page 44, line 16.

Additional working examples of measuring DGAT and MGAT activity are provided in Example 5. Specification, page 46, line 11 to page 47, line 10. For example, the enzymatic activity of MGAT polypeptides (e.g., SEQ ID NOs:06) were assayed. Example 5. Accordingly, an actual working example has been disclosed in the specification.

(f) the relative skill of those in the art:

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

(g) the predictability or unpredictability of the art

Those skilled in the art are well aware of how to predict whether a given amino acid sequence, if altered, e.g., by conservative or non-conservative amino acid substitutions, would retain the activity of a

[6] In re Borkowski, 164 USPQ at 645.
[7] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

given reference polypeptide. For example, by aligning amino acid sequences of related polypeptides, e.g., polypeptides that share an enzymatic activity, those of ordinary skill in the art can readily predict amino acid substitutions that will likely not alter enzymatic activity, and those that likely will.

While there may be some non-functional variants within the genus defined by sequences 90% or more identical to SEQ ID NO:03, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

The claims of the instant application encompass polynucleotides with 90% or more sequence identity to SEQ ID NO:03. Since one of skill in the art would recognize that a reasonable correlation exists between the activities of polypeptides in this genus, and since every species in a genus does not have to be tested for a genus to be enabled, extensive disclosure or guidance of the active species of a genus does not have to be provided for a genus of this scope to be enabled.

(h) the breadth of the claims

The claims of the instant application encompass sequences that exhibit monoacylglycerol acyltransferase and/or diacylglycerol acyltransferase. In other words, in order to fall within a claim, a sequence must be able to catalyze the transfer of an acyl group to a monoacylglycerol and/or a diacylglycerol. *Thus, the claim language excludes polynucleotides encoding polypeptides that do not exhibit this activity.*

[8] *In re Angstadt*, 190 USPQ at 218.

In sum, the amount of experimentation required to identify polynucleotides comprising nucleotide sequences that are 90% or more identical to SEQ ID NO:03 would not be undue because a) a working example has been provided, b) guidance is given on how to test the sequences has been provided, c) there is a good correlation between the activities of species within a genus of this breath, and d) one of skill in the art would be able to perform the experiments as a matter of routine to determine the active sequences.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended to recite "95% nucleotide sequence identity to the sequence set forth in SEQ ID NO:03." The arguments set forth above also apply to amended claim 1.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1, 2, 7-10, and 24-27 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(a)

Claims 1, 2, 7-10, 26, and 27 were rejected under 35 U.S.C.§102(a) as allegedly anticipated by WO 00/12708 ("Baker").

Without conceding as to the correctness of this rejection, claim 1 is amended to recite "95% nucleotide sequence identity to the sequence set forth in SEQ ID NO:03."

Applicants submit that the rejection of claims 1, 2, 7-10, 26, and 27 under 35 U.S.C. §102(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL240CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Aug. 10, 2004

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